control in this population. Specifically, it is unknown whether the normal nocturnal decline in BP is present in patients with LVAD.

METHODS: Twenty-four hour ambulatory BP and LVAD rate were measured in 10 patients (six males/ four females, mean age 54 ± 13 years) who had received a LVAD for cardiogenic shock. Etiology of cardiac dysfunction was ischemic in four patients, non-ischemic in five patients, and hypertrophic in one patient. Patients were clinically stable out of the intensive care unit and were not on inotropic support. Nine of the patients were on anti-hypertensive therapy.

RESULTS: When comparing daytime and nighttime mean readings, there was no significant change in systolic, diastolic, or mean BP or in LVAD rate.

CONCLUSION: Similar to patients with congestive heart failure or cardiac transplantation, patients with LVAD lack a normal nocturnal decline in BP. This abnormal pattern of BP increases the cumulative work of the device by continuous 24 hour exposure to high afterload. Therefore, more aggressive treatment of hypertension in patients with left ventricular assist devices may be warranted to reduce the long-term workload of the device.

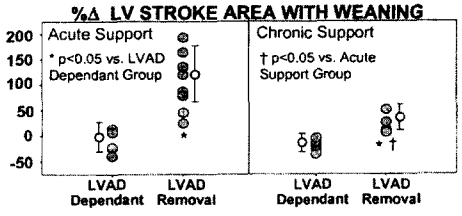
Vital Sign	Day (8AM-8PM)	Night (12AM-6AM)	p Value
Systolic Blood Pressure (mm Hg)	125 ± 10	120 ± 12	NS
Diastolic Blood Pressure (mm Hg)	72 ± 11	69 ± 10	NS
Mean Arterial Pressure (mm Hg)	90 ± 8	87 ± 9	NS
LVAD Rate (beats/min)	75 ± 19	75 ± 20	NS

10:15 a.m.

808-5 **Identification of Left Ventricular Recovery on Mechanical Assist Devices: Acute Support for Postcardiotomy Shock Versus Chronic Support as a Bridge to Transplant**

John Gorcsan, III, Donald A. Severyn, Bartley P. Griffith, Robert L. Kormos, *University of Pittsburg, Pittsburg, Pennsylvania.*

Left ventricular assist devices (LVAD) can be life saving for acute heart failure (HF) associated with post-cardiotomy shock and also severe HF as a bridge to transplant. To test the hypothesis that quantitative echo measures can detect LV recovery on LVAD support, 23 pts were studied: 11 with LVAD for acute post-cardiotomy shock (support duration 5±1 d) and 12 with LVAD as bridge to transplant (support 276±191 d). Acute devices were 6 Abiomed, 5 Biomedicus. Chronic devices were 6 Novacor, 6 Thoratec. LV end-diastolic and end-systolic area measures were made during full VAD support (acute flow=4.5±0.5, chronic flow=6.1±1.3L/min) and during decreases in VAD flow (acute flow=1.6±0.6,chronic flow=3.0±0.6L/min). 8 patients with acute support and 4 with chronic support had successful LVAD removal and survived to hospital discharge. Significant differences were observed between the LV recovery patients on acute vs. chronic support as follows: % δ in LV fractional area change (acute=77±55% vs chronic=-3±10%,p<0.05) and %δ in stroke area (acute=105±54% vs chronic=19±18%,p<0.05) following weaning to low flow. **Conclusions** Quantitative echo detected LV recovery and predicted successful device removal in patients on both acute and chronic LVAD support. Recovery from acute shock was associated with greater degrees of LV functional improvement than patients on chronic support. Separate criteria need to be used to govern the removal of devices with respect to duration of mechanical circulatory support.



ORAL CONTRIBUTIONS

810 Heart Failure Trials I

Monday, March 18, 2002, 11:00 a.m.-12:15 p.m.
Georgia World Congress Center, Auditorium

11:00 a.m.

810-1 **Testosterone Therapy Improves Exercise Duration and Symptoms in Men With Chronic Congestive Heart Failure**

Peter J. Pugh, John N. West, T. Hugh Jones, Kevin S. Channer, *Department of Cardiology, Royal Hallamshire Hospital, Sheffield, United Kingdom, Institute of Endocrinology, University of Sheffield Medical School, Sheffield, United Kingdom.*

Background: Chronic heart failure (CHF) remains a major cause of morbidity, with terrible prognosis. Relative androgen deficiency reported in men with CHF could contribute to the pathophysiological processes of myocardial dysfunction, neuro-hormonal activation, catabolic excess and muscle wasting and therefore to symptoms of exercise intolerance and dyspnoea. We examined the effects of androgen therapy on exercise duration, symptoms, cardiac function and skeletal muscle strength and bulk in men with CHF.

Methods: In a double-blind trial, 20 men with CHF (age 61.5±8.5 years, ejection fraction 34.8±7.8%) were randomised to 3 months treatment with testosterone 100mg or placebo by fortnightly intramuscular injection. Exercise tolerance was assessed by the incremental shuttle walk test; symptoms by NYHA class, Minnesota Living with Heart Failure (MLHF) score and Beck Depression Inventory (BDI); cardiac function by echocardiography. Skeletal muscle bulk was estimated by CT-computed cross-sectional area of mid-thigh and mid-calf muscle; hand-grip strength was measured by dynamometry. Data are as mean±SD and were analysed by Wilcoxon matched pairs and Mann-Whitney U test.

Results: Baseline characteristics did not differ significantly between groups. Mean testosterone level at baseline was 12.7±6.4nM (normal range 10-37nM). Exercise distance increased markedly in the active treatment group (from 328±174m to 419±200m, p=0.01) but not in the placebo group (from 314±92m to 340±101m, p=0.12). The increase in walk distance in the two groups differed significantly (28% *v* 8% increase, p=0.015). NYHA class improved with treatment (from 2.3±0.5 to 1.9±0.7, p=0.046), as did MLHF score (34.5±29.2 to 26.5±25.2, p=0.05) and BDI score (7.3±7.3 to 5.7±6.0, p=0.03). There were no changes in left ventricular function or in measures of skeletal muscle bulk and grip strength.

Conclusion: In a pilot study, testosterone therapy for men with chronic heart failure improved exercise duration, symptom scores and mood with no apparent effect on LV function or skeletal muscle and no reported adverse effects. This may prove a useful add-on therapy for improving functional capacity and symptoms in these patients.

11:15 a.m.

810-2 **Effect of Carvedilol on Major Clinical Events in Patients With Severe Heart Failure and an Extremely Depressed Ejection Fraction: Results of the COPERNICUS Study**

Hugo A. Katus, Michal Tendera, Paul Mohacsi, Jean L. Rouleau, Michael B. Fowler, Andrew J. Coats, Henry Krum, Terry L. Holcslaw, Ellen B. Roecker, Milton Packer, for the COPERNICUS Study Group., *Universitaets-Klinikum Luebeck, Luebeck, Germany.*

Background: Despite the demonstrated survival benefit of β-blockers in heart failure (HF), many physicians avoid the use of these drugs in patients with extremely depressed LV function in the belief that they will not respond favorably or may be adversely affected by treatment.

Methods: Of the 2289 patients with severe HF enrolled in the COPERNICUS trial, 371 patients had a baseline LV ejection fraction <= 15%. These patients had a lower mean systolic blood pressure (117 vs 125 mm Hg) and were more likely to be treated with digitalis (73% vs 65%) than patients with higher EF (both P<0.002) but were otherwise similar in their baseline characteristics. Both subgroups of patients were randomized to placebo (PBO) or carvedilol (CRV) for up to 29 months.

Results: Shown below are 1-year Kaplan-Meier rates and risk reductions with CRV (Cox model).

	Ejection fraction <= 15%			Ejection fraction > 15%		
	PBO (n=191)	CRV (n=180)	Reduction in risk	PBO (n=942)	CRV (n=976)	Reduction in risk
All-cause mortality	23.8%	18.9%	30%	17.4%	9.7%	36%
Death or hospitalization for worsening HF	46.3%	30.3%	39%	36.0%	24.6%	28%
Death or cardiovascular hospitalization	52.1%	34.6%	41%	39.4%	29.4%	23%
Death or any hospitalization	59.9%	47.2%	33%	50.7%	40.4%	21%

The effects of CRV on all-cause mortality and on the risks of death or hospitalization (for any reason or for a specific cause) in patients with EF <= 15% were similar to those seen in patients with higher EF. CRV reduced the risk of permanent discontinuation of study drug in patients with EF <= 15% (by 32%) and in those with higher EF (by 19%).

Conclusion: CRV is effective and well tolerated even in patients with severe HF symptoms and an extreme depression of LV systolic function.

11:30 a.m.

810-3 **Nutritional Supplementation With MyoVive® Repletes Essential Cardiac Myocyte Nutrients and Reduces Left Ventricular Size in Patients With Left Ventricular Dysfunction**

Farida Jeejeebhoy, Mary Keith, Michael Freeman, Aiala Barr, Michele McCall, Regina Kurian, David Mazer, Lee Errett, *St. Michael's Hospital, Toronto, Ontario, Canada, University of Toronto, Toronto, Ontario, Canada.*

Background: Congestive heart failure (CHF) depletes the myocardium of carnitine, coenzyme Q10 (CoQ10) and taurine, substances known to influence mitochondrial function and cell calcium. We hypothesized that feeding patients a nutritional supplement which contains carnitine, CoQ10 and taurine would result in higher myocardial levels and improve left ventricular function.

Methods: Forty-one aortocoronary artery bypass patients with an ejection fraction (EF)< 40% at referral, were randomized to a double-blind trial of supplement (S) or placebo (P). Radionuclide ventriculography was performed at randomization (R) and just prior to surgery. Surgical myocardial biopsies, adjusted for protein content, were analyzed for carnitine, CoQ10 and taurine levels.

Results: The groups were well matched. Minor exceptions were S vs P for digoxin use (7 versus 0 respectively p=0.0087) and age (62±11 versus 69±5 respectively, p=0.0395). There were significantly higher levels in the treated as compared to the placebo group for

myocardial levels of CoQ10 (138.17±39.87 and 56.67±23.08 nmols/g wet weight [p=0.0006]), taurine (13.12+4.00 and 7.91±2.81 umol/g wet weight [p=0.0016]), and carnitine (1735.4+798.5 and 1237.6+343.1 nmol/g wet weight [p=0.056 and p=0.028 one tailed]). The left ventricular end diastolic volume (LVEDV) fell by -7.5+21.7 in the supplemented group and increased by 10.0+19.8 in the placebo fed patients (p=0.037).
Conclusions: Supplementation results in higher myocardial CoQ10, taurine and carnitine levels and is associated with a reduction in LVEDV in patients with left ventricular dysfunction prior to revascularization. Since the risk of mortality for surgical revascularization is related to preoperative LVEDV, supplementation could improve outcomes.

11:45 a.m.

810-4 Vasopressin Receptor Blockade in Patients With Congestive Heart Failure: Results From a Placebo Controlled, Randomized Study Comparing the Effects of Tolvaptan, Furosemide, and Their Combination

James E. Udelson, Cesare Orlandi, Terrence O'Brien, Rafael Sequeira, John Ouyang, Marvin A. Konstam, *Tufts-New England Medical Center, Boston, Massachusetts.*

Background: Increased vasopressin levels contribute to the progression of heart failure (HF) to an unknown degree. The presence of diuretics has confounded prior evaluations of vasopressin receptor antagonists (VRA). We investigated the effects of VRA in the absence of a diuretic for the first time, with Tolvaptan (OPC-41061, TLV), a novel, nonpeptide VRA.
Methods: Pts with HF (NYHA class II-III, n=83) and signs of congestion (e.g., edema or rales) were removed from baseline diuretic therapy and placed on a low-sodium diet (2g/day). After a 2-day run-in period, pts were randomized to placebo (n=21), monotherapy with TLV 30mg (n=20), monotherapy with furosemide (FURO) 80mg (n=22), or both TLV and FURO (n=20) once daily for 7 days. Pts were on standard background therapy and not fluid restricted.
Results: TLV was well tolerated. Table: Changes in body weight and urine volume on last study day. An increase in serum Na within the normal range was observed in TLV-treated pts (p<0.02 vs placebo; p<0.01 vs FURO). No changes in serum potassium, other lab values or BP were observed. Reductions in leg edema, dyspnea, JVP, rales and hepatomegaly were also noted in the TLV-treated pts versus placebo.
Conclusions: In pts with HF and signs of volume overload, TLV monotherapy without concomitant loop diuretic therapy reduced body weight and lessened edema when compared to placebo, without adverse changes in serum electrolytes. These findings support a potential therapeutic role of inhibiting vasopressin excess in pts with HF.

Change from baseline:	Placebo	TLV	FURO	TLV+FURO
Body Wt (kg)	+0.72±2.42	-1.37±1.61*	-0.54±1.59	-1.13±1.49*
Urine output (ml/24hr)	+423±786	+2646±1503*+	+894±853*	+2585±2119*+

* p<0.01 vs baseline
\+ p<0.001 vs FURO

Noon

810-5 Impact of BEST and COPERNICUS on Overall Estimates of Beta-Blocker Survival Benefit in Heart Failure: An Updated Meta-Analysis of Randomized Trials

David J. Bradley, Neil R. Powe, Kenneth L. Baughman, *Johns Hopkins Hospital, Baltimore, Maryland.*

Background: Previous meta-analyses have shown a reduction in mortality among heart failure patients treated with beta-blockers. These meta-analyses, however, did not include the results of the recently published Beta-Blocker Evaluation of Survival Trial (BEST), a large study which did not demonstrate improved survival among heart failure patients treated with beta-blockers. In order to assess the impact of BEST on the overall estimated efficacy of beta-blockers in symptomatic heart failure, we conducted a meta-analysis. We also included the recently published Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) in our meta-analysis.
Methods: Medline and the Cochrane Controlled Trials Register were searched for randomized controlled trials comparing beta-blockers versus placebo among patients with symptomatic left ventricular systolic dysfunction. Twenty-six randomized trials that enrolled 15,369 patients were identified. Trials were reviewed independently by two raters. Abstracted data included patient exclusion criteria, patient baseline characteristics, trial interventions, trial outcomes, and trial quality.
Results: Trials were published between 1985 and 2001. Ten trials randomized patients to metoprolol, and 9 to carvedilol. Baseline ejection fraction ranged from 16% to 34%. BEST recorded nearly as many deaths (860) as 24 previously published trials combined (1094). Using a random effects model, the pooled odds ratio of death among patients treated with beta-blockers versus placebo in 24 trials published before BEST and COPERNICUS was 0.65 (95% confidence interval (CI) 0.57 - 0.74). Pooling of mortality data from BEST with these previously published 24 trials increased the odds ratio of death from 0.65 to 0.73 (95% CI 0.66 - 0.81). Inclusion of mortality data from both BEST and COPERNICUS in the meta-analysis yielded an odds ratio of death of 0.71 (95% CI 0.65 - 0.78).
Conclusion: Although BEST was a large trial with a negative mortality endpoint, it has only modestly diminished the overall estimated survival benefit of beta-blockers in the treatment of symptomatic heart failure.

ORAL CONTRIBUTIONS

813 Inherited Cardiomyopathy

Monday, March 18, 2002, 11:00 a.m.-12:15 p.m.
Georgia World Congress Center, Hall D2

11:00 a.m.

813-1 Spironolactone Reverses Myocyte Disarray and Interestitial Fibrosis in the Cardiac Troponin T Transgenic Mouse Model of Hypertrophic Cardiomyopathy

Rajnikant Patel, Shintaro Nemoto, Gilberto DeFreitas, Tripti Halder, Silvia Lutucuta, Natalia Tsyboulev, Lorraine Salek, Robert Roberts, Blase Carabello, Ali J. Marian, *Baylor College of Medicine, Houston, Texas.*

Hypertrophic cardiomyopathy (HCM), the most common cause of sudden cardiac death (SCD) in the young, is caused by mutation in sarcomeric proteins. It is characterized by hypertrophy, myocyte disarray, and interstitial fibrosis. We have proposed that hypertrophy, disarray, and fibrosis, major predictors of SCD, are secondary to activation of trophic/mitotic factors and intracellular signaling kinases, and thus, are reversible. We performed a randomized study to determine the effects of blockade of aldosterone, a major mitotic and pro-fibrotic factor, on cardiac phenotypes in the cardiac troponin T-glutamine92 (cTnT-Q92) transgenic mice, shown to exhibit significant myocyte disarray and interstitial fibrosis. We randomized 26 adult cTnT-Q92 mice to treatment with spironolactone (50 mg/kg/d) or placebo (olive oil) for 10 weeks and included 13 non-transgenics (non-tg) as controls. We performed M-mode, 2D, and Doppler echocardiography prior to and at the completion. There were no significant differences in body weight, heart weight, their ratio, male/female ratio, mean age, and heart rates among the three groups. Myocyte disarray in non-tg, placebo, and spironolactone groups were 4.4±2.0, 22.8±9.8, 10.2±3.1 % of the myocardium, respectively (p<0.001). Collagen volume fraction were (3.4±1.9, 7.2±5.9, and 2.8±0.9%, respectively p=0.001). Left ventricular end diastolic diameter was smaller (4.3±0.4, 4.1±0.3, 3.9±0.2, p=0.008) and E/A ratio was improved in spironolactone group. Wall thickness and fractional shortening were unchanged. Expression levels of activated, but not total, ERK1/2 were increased in the placebo and was normalized in spironolactone groups. Levels acticated p38 kinase, JNKs, GTP-bound and total Ras, Rac and Rho were unchanged. A duplicate study (n=8 mice per group) connfirmed the results and showed a 50% reduction in myocyte disarray and fibrosis with spironolactone. Thus, myocyte disarray and interstitial fibrosis, the pathological hallmarks of HCM and major predictors of SCD, could be reversed with aldosterone antagonist, spironolactone. These results in a genetic animal model of HCM, beckons clinical studies in human patients with HCM.

11:15 a.m.

813-2 Clinical Markers for the Identification of Gene Carriers in Naxos Disease Families

Nikos Protonotarios, Adalena Tsatsopoulou, Aris Anastasakis, Elias Sevdalis, Artemisia Theopistou, Antigone Miliou, Angelos Rigopoulos, Evangelia Karvouni, Christodoulos Stefanadis, Pavlos Toutouzas, *Cardiology Dept., University of Athens, Athens, Greece, Yiannis Protonotarios Medical Center, Naxos, Greece.*

Background: Naxos disease is a syndrome of arrhythmogenic right ventricular cardiomyopathy (ARVC) with autosomal recessive inheritance. The responsible pathogenic gene is that of plakoglobin, a constituent of the cardiac and skin cells desmosomes and adherence junctions. We genotyped patients and members of ARVC families trying to identify the clinical characteristics of each genotyped group (homozygous, heterozygous, normals).
Methods: We studied 78 individuals from 12 families (28 patients and 50 family members without the stereotype phenotype). Genetic screening involved DNA extraction from venous blood, multiplication of a 2Kb area around the PK2157del2 site of the gene (where the mutation appears by deletion of 2 bases) by using polymerase chain reaction with specifically designed primers. Restriction enzyme analysis, using the restriction endonucleaseBst01, verifies the presence or not of the mutation. Clinical assessment involved clinical examination, electrocardiography and echocardiography. We performed sensitivity-specificity analysis in order to identify specific clinical markers for the gene carriers.
Results: All 28 Naxos ARVC patients were homozygous for the PK2157del2. Among 50 family members without the stereotype phenotype, 40 were gene carriers (heterozygous) and 10 possessed normal alleles. Curly hair was present in all 28 Naxos ARVc patients, in 15 of the 40 gene carriers and in none of the normals (specificity 100%, sensitivity 37.5% for the heterozygous). Palmoplantar keratoderma was only present in all homozygous (patients). T wave inversion in lead V3 was present in 20/28 patients, 1/40 heterozygous and 0/10 normals (specificity 100%, sensitivity 2.5% for the heterozygous). Right ventricular outflow tract (RVOT) dilatation (>31mm) was present in 15/28 patients, 3/40 heterozygous and 0/10 normals (specificity 100%, sensitivity 53.5% for the heterozygous).
Conclusion: All Naxos disease patients were homozygous for the plakoglobin gene mutation. Curly hair, T wave inversion and RVOT enlargement seem to be specific markers for identifying the gene carriers among the members of Naxos ARVC families.